CUTANEOUS SMEARS: A DIAGNOSTIC AID IN CERTAIN MALIGNANT LESIONS OF THE SKIN*

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Microscopic examination of conventionally cut and stained sections of excised cutaneous tumors usually permits details of the larger tissue cells to be seen clearly enough to allow one to make an accurate diagnosis except in certain instances. However, in leukemic infiltrations into the skin, when the specific diagnosis rests on the identification of smaller cells that have arisen within or infiltrated into the skin, the most carefully cut and stained sections of skin do not show these small cells with sufficient clarity to permit their identification. This difficulty arises from two factors: (1) the cells in the block of tissue are shrunken and distorted due to the action of fixatives and solvents used in the preparation of the tissue for examination and (2) the cells to be identified lie compressed in different planes in the interstices of the tissue spaces.

An undistorted preparation of the infiltrating cells spread in a single plane is achieved by the use of imprints of the involved tissue. The afore-mentioned distorting factors found in the preparation of sections of skin are thus eliminated.

GENERAL BACKGROUND

Imprints of tissue have been used previously for the study of other tissues. Smears have been made from the tissue directly or from cells exfoliated from the surface of the organ being investigated. Examples of the former method are smears made from elements aspirated from bone marrow and impression smears of the cut surfaces of lymph nodes. Exfoliated cells from the vagina, uterus, esophagus, stomach and the respiratory and urinary tracts have been studied by the smear method. Nanta and Chatellier (1), in 1925, presented 2 cases in which smears as well as sections were made from tissue obtained from lesions of the hand and tongue. The smears were treated with the May-Grünwald-Giemsa stain and revealed cells which permitted the investigators to make the diagnosis of "lymphogranulomatosis," or Hodgkin's disease. Montgomery and Watkins (2), in 1937, described a case of monocytic leukemia and reported that smears made from a cutaneous plaque and smears of the peripheral blood revealed identical cells. Later reports by the same workers dealt with this problem (3, 4). Sweitzer and Winer (5), in 1945, described a technic for making smears of tissue and pictured imprints of lymph nodes in a case of Hodgkin's disease. Winer (6),

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in 1947, discussed 4 cases of mycosis fungoides and published a photomicrograph of a malignant reticulum cell in an imprint from a cutaneous tumor in mycosis fungoides.

Tzanck and associates (7), in 1948, reported their experience with smears and stressed the speed with which the smear could be prepared and examined; however, they used the technic chiefly in cases in which the diagnosis could be established better by study of the usual stained section. They considered that the method was most important in cutaneous epitheliomas but admitted that they could not differentiate with certainty the various types of such tumors.

PRESENT STUDY

In order to evaluate the cutaneous smear as an aid in the cytologic diagnosis of dermal lesions, touch smears were made at the time of biopsy in each of 176 cases in which specimens of skin were excised for histopathologic examination; the first 123 of these cases were studied at the Mayo Clinic. The subsequent 53 cases came under my observation and the complete study covered a period of 5 years. Several problems were involved in this work. It was necessary (1) to develop a simple technic of smearing and staining specimens, (2) to determine which elements of the skin appeared consistently in the smears, (3) to become familiar with the appearance of normal and abnormal cells and (4) to define the assets and limitations of cutaneous smears. To accomplish the latter, the imprints of tissue were compared with the usual sections of tissue prepared by means of a microtome.

TECHNIC

The specimen of skin is removed by excision or by a cutaneous punch. The piece of skin is cut immediately with a scalpel in a plane perpendicular to the cutaneous surface and through the region of pathologic change. The freshly cut surface of one of the halves of tissue is then pressed lightly on a clean glass slide. The specimen is lifted and then again pressed to the slide in a new area, gently smeared for a third of the length of the slide and again lifted. This process of making both an imprint and then a smear is repeated. Two or three rows of such impressions are quickly made on a slide. Then the film is dried immediately by waving the slide in the air. Several slides are smeared in this manner, using both halves of the specimen of skin. If examination of the cut surfaces of the tissue fails to reveal evidences of gross infiltration as expected from the clinical appearance of the lesion, further sections through the tissue, with smears from these, are made. This is done to allow maximal concentration of cells in the film. After the impressions are made, the tissue is placed in a 10 per cent solution of formalin to be processed in the usual manner.

The air-dried smears are stained in Wright's stain for 1½ minutes; buffer solution is then added and allowed to act for 5 minutes. The slides are washed and dried for examination under the microscope.

The wet-smear technic, employing the method of fixation of Dudgeon and Wrigley or that of Papanicolaou, in which the smears are immersed in a fixative without being allowed to dry, provides excellent fixation for staining with hematoxylin and eosin. However, imprinted cells often wash off the slide when it is immersed in the ether-alcohol solution unless they are firmly held by means of albumin coated on the surface of the slide. The staining procedures employed with wet smears, with multiple passages through various solutions, are complicated and time-consuming. Special stains to demonstrate unusual cellular characteristics usually can be applied to the air-dried films with the same facility as encountered in films preserved in fluid.

Wright's stain was used routinely in this study because of its simplicity and the ease with which connective-tissue cells and infiltrating cells absorb the stain. Other methods, such as the Schiff periodic acid technic and use of mucicarmine, were used to show special properties of certain cells.

RESULTS

Cutaneous smears were made concomitantly with sections of skin in 52 distinct types of cutaneous disease. Results of the smears were interpreted as normal or nonspecific in 135 instances. In 41 cases, study of the smears resulted in the diagnosis of a specific neoplastic disease. The diagnosis in 15 of these cases was more specific than could be determined by study of sections of skin alone. Smears failed to show the presence of neoplastic cells in 7 cases in which malignant disease was present; these cases included 6 of mycosis fungoides and 1 of Hodgkin's disease. In these 7 cases, tissue was obtained after partial or complete regression of the lesions as a result of x-ray therapy or use of nitrogen mustard. It is possible that the smears were made from tissue which did not contain neoplastic cells.

It was found that cells infiltrating into the parenchyma of the skin are transferred readily from the cut surface of the tissue to the slide, thus permitting these cells to be seen free and undistorted by the surrounding tissue.

Cutaneous smears from diseases whose lesions are not characterized by infiltration of abnormal cells revealed erythrocytes, lymphocytes, blood and tissue leukocytes, histiocytes and fibers of collagen and elastin. Nonmalignant conditions marked by increased cellular infiltration produced cutaneous smears containing chiefly histiocytes, leukocytes or lymphocytes (fig. 1*a* and *b*).

CELLS ENCOUNTERED IN CUTANEOUS SMEARS

The term "histiocyte" is used to describe the free and fixed wandering cells of the loose connective tissue and the histioid cells of the blood. These cells are under continuous physiologic stimulation and take an active part in inflammatory and certain neoplastic processes in the skin. These cells, of mesenchymal origin, have been known by a confusing variety of names given by investigators according to the function attributed to these cells at the time of investigation. Synonyms are "macrophage," "polyblast," "hemohistiocyte," "clasmatocyte" and "resting wandering cell." While typical monocytes and histiocytes have morphologic characteristics that distinguish each cell when seen in smears of bone marrow or blood, the distinction between these two cells was difficult to establish in smears from the skin.

The histiocyte in cutaneous smears stained according to Wright's method (fig. 1*b*) was characterized by a relatively large nucleus, which ranged from 14 to 22 microns in length in the sessile forms and was slightly smaller in the rounded mobile cells. The nuclei in the resting forms contained loosely reticulated, light-staining chromatin; the nuclei in the smaller mobile histiocytes contained denser chromatin that stained a deeper shade of blue. One or more vesicular nucleoli were usually present. The nuclear membrane was oval or reniform and occasionally folded. The cytoplasm was light blue with a faint outline and varied in amount. Various types of inclusions were present.

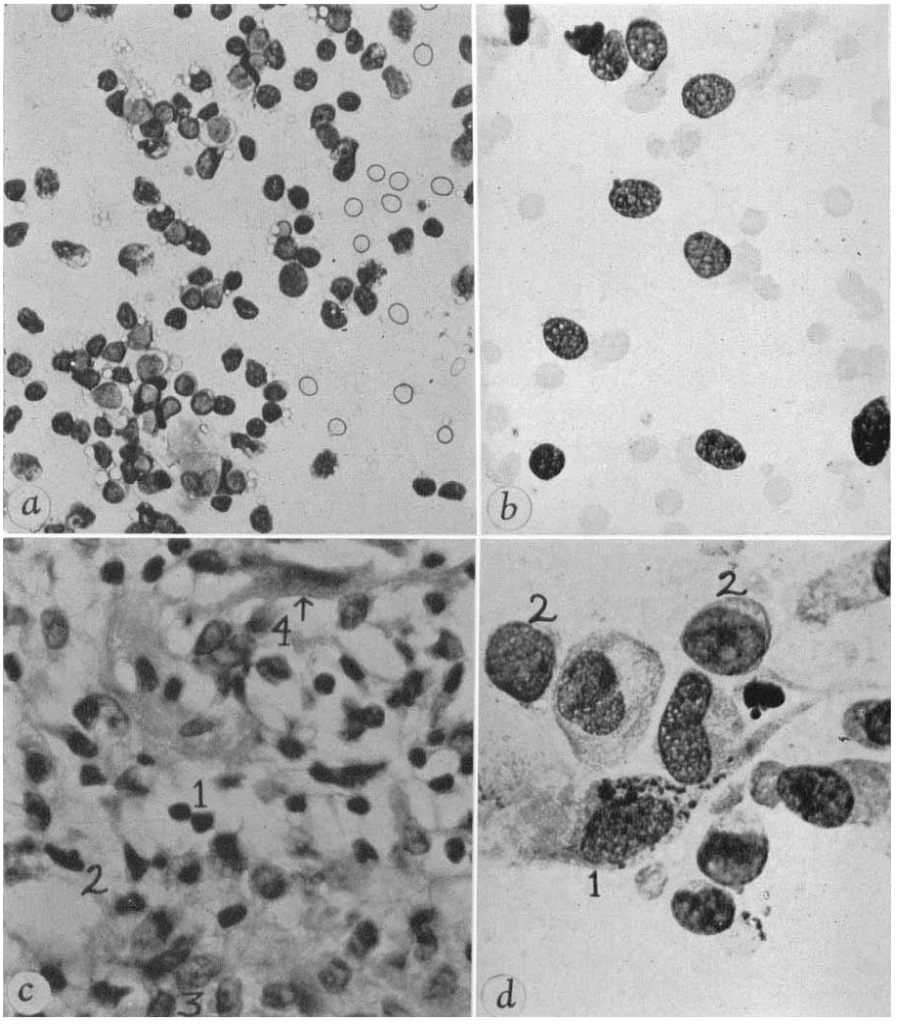

FIG. 1*a*. Normal cells in a cutaneous smear obtained in a case of rosacea. Small, medium and large lymphocytes predominate, with increase in the number of normal-appearing histiocytes; few erythrocytes are noted (Wright's stain; ×275). *b*. Cutaneous smear showing increase in the number of normal-appearing histiocytes due to inflammation (Wright's stain; ×500). *c* (Case 1). Section of skin in mycosis fungoides. Note small dark-staining lymphocytes (1) and larger cells (2); cells with large nuclei and one or more dark nucleoli (3) are epithelioid cells. A probable fibroblast (4) is present (hematoxylin and eosin; ×515). *d*. Cutaneous smear in same case. Note histiocyte (1) containing phagocytized dark-staining particles. Other histiocytes (2) have lighter-staining vesicular nucleoli with large nuclei in relation to cytoplasmic volume; this suggests immaturity (Wright's stain; ×720).

Malignant cells could be distinguished from normal cells in cutaneous smears by numerous characteristics according to the type of abnormal cell. Immaturity of cells of the lymphoid, myeloid and histiocytic series was evidenced by large cells having large nucleoli. Some cells showed secretory activity or melanogenesis.

Malignant cells in cutaneous smears showed the characteristic structure of malignant growth seen in other tissues. Usually the cells could be identified as being related to a specific series of cells, such as the lymphocytic, myelogenous or histiocytic series, or they showed characteristics of squamous or glandular epithelium.

Blast cells were the most acutely malignant mesenchymal cells encountered in cutaneous smears. The blast cell, or stem cell, was large (15 to 30 microns in diameter), with a large nucleus in proportion to the amount of cytoplasm; the latter appeared as a pale-blue rim about the nucleus. The nuclear chromatin was extremely fine, staining lighter than the relatively coarse chromatin of a more mature cell. Several distinctly outlined pale nucleoli were present. If the infiltrate contained an insufficient number of differentiated cells, giving no clue to the series into which the blast cell was to differentiate, the only diagnosis possible was that of infiltration with acute blast cells. Since sarcoma is the proper term for malignant lesions of mesenchymal origin, the diagnosis of blast cell sarcoma might be proposed.

Blast cells may differentiate into lymphocytes, granulocytes, monocytes or plasma cells. When sufficient evidence for such differentiation was present in the smears, the diagnosis was more specific.

Malignant growths involving the histiocytic series of cells were characterized by an infiltrate of cells rather closely resembling normal histiocytes. These cells frequently predominated in the smear to the exclusion of other cellular types. The immature cell had a large nucleus containing finer chromatin and larger, more distinct, vesicular nucleoli than were found in the mature histiocyte. The cytoplasm stained a deeper blue and sometimes contained inclusions or vacuoles. In certain malignant conditions, cells of the histiocytic series appeared to be pleomorphic and to be undergoing nuclear division. The resulting cells had characteristics ranging from lobed dark-staining nuclei with or without nucleoli to multinucleated giant cells of the Sternberg-Reed type.

Metastatic carcinomatous cells in cutaneous smears were distinct in appearance from the malignant cells just described. Metastatic cells were usually larger and the nucleus was large in proportion to the cytoplasm. The nuclear chromatin stained darkly and was coarse. Dark, large, often multiple nucleoli were present. The cytoplasm was distinctly outlined and stained darkly with Wright's stain. Metastatic cells in the same stages of development often appeared in clumps, presenting an infiltrate of a constant cellular type. This characteristic varied according to the degree of malignancy. Squamous cells frequently varied in size, shape and staining reaction, making broad descriptive generalizations misleading. Cells that have metastasized from adenocarcinoma may have eccentric nuclei as a result of displacement by globules of mucinous substance secreted in the cytoplasm of the cells.

In general, immaturity was not seen in the infiltrating cells in smears made from normal skin. In sections of skin, mitotic figures were seen normally in a small proportion of cells in the malpighian layer. Epithelial cells occurred infrequently in cutaneous smears and epithelial cells undergoing mitosis were not seen in smears from nonmalignant dermal lesions made in this study.

A group of cases illustrative of some of these observations now will be presented. All of these cases were encountered at the Mayo Clinic.

REPORT OF REPRESENTATIVE CASES

Case 1.—A 31-year-old woman had noted onset of erythroderma 2½ years before she came to the clinic. A year after onset, macules, nodules and infiltrated plaques measuring up to 5 cm. in diameter appeared in the skin. At this time a clinical and histopathologic diagnosis of mycosis fungoides was made. In the next 16 months, the patient benefited from repeated alternating courses of x-rays and nitrogen mustard.

The biopsy and smear included in this study were done 2 months after the last exposure to x-rays; the material used came from a persisting tumor in the skin of the shoulder. Examination of the patient at this time showed the abnormalities to be limited to the skin, which was dry and slightly lichenified. Several infiltrated plaques, measuring up to 4 cm. in diameter, were scattered over the entire body. These were mostly in the stage of involution as the result of x-ray therapy. The only laboratory finding of note was moderate intermittent eosinophilia.

Study of sections revealed dense infiltration of cells occupying the upper portion of the dermis. This infiltrate included epithelioid cells, small, dark-staining lymphocytes, leukocytes, eosinophils and connective-tissue cells (fig. 1*c*). Cutaneous smears disclosed that some histiocytes contained phagocytized dark-staining particles in their cytoplasm (fig. 1*d*). The mobile histiocytes were similar to those seen in inflammation.

In untreated mycosis fungoides, however, these cells have light-staining vesicular nucleoli and a large nucleus in relation to cytoplasmic volume. This is indicative of immaturity and suggests that mycosis fungoides is a sarcoma of low degree of malignancy, placing it in the group that includes reticulum cell sarcoma and Hodgkin's sarcoma.

Case 2.—A 50-year-old man complained of a universal eruption of 7 months' duration. The lesions consisted of discrete reddish-brown infiltrated nodules that ranged up to 1 cm. in diameter. The patient was obese and exhibited bilateral inguinal adenopathy. The edge of the liver was tender but the organ was not enlarged. Hematologic studies revealed no significant abnormalities.

Sections of the skin showed some disintegration of the basal cell layer by infiltrating cells. This infiltrate was composed of lymphocytes, rather large mononuclear cells and epithelioid cells (fig. 2*a*). The infiltrating cells were chiefly in the upper part of the dermis but they extended almost to the subcutis. A few scattered mitotic figures were present. The infiltrating cells had relatively large dark-staining nuclei and appeared to be wedged between the epithelioid cells.

Cutaneous smears showed that these infiltrating cells were large and had abundant light-blue cytoplasm; the nuclei were large and contained loosely reticulated chromatin that appeared blue with Wright's stain (fig. 2*b*). These cells apparently were adult reticulum cells. A number of hemocytologists who examined these smears remarked on the similarity of these cells to the reticulum cells of normal bone marrow. These connective-tissue cells appeared to be more mature than the cells that were infiltrating the dermis in case 1. A diagnosis of reticulum cell sarcoma was made.

The patient subsequently received several courses of nitrogen mustard given intravenously, with improvement in health and regression in the cutaneous nodules. The nodules returned within several months after each treatment, with successively shorter periods of remission; superficial x-ray therapy to the skin was given in order to control the symptoms.

Case 3.—A 46-year-old woman had been ill for 2 years with cervical and inguinal adenopathy. Six months prior to examination, after x-ray therapy to the enlarged lymph

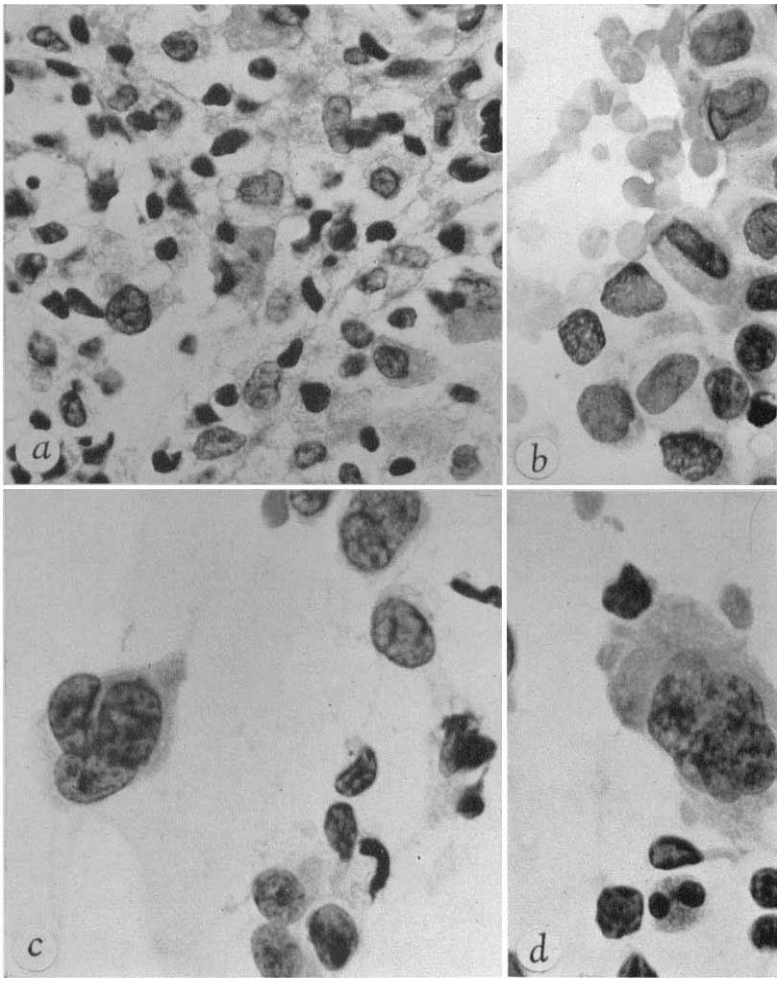

FIG. 2*a* (Case 2). Section of skin in reticulum cell sarcoma. Note epithelioid cells with large nuclei and dark nucleoli; the smaller cells with dark nucleoli are abnormal infiltrating cells (hematoxylin and eosin; ×580). *b*. Cutaneous smear in same case. The nuclei and cytoplasm of the infiltrating cells are more clearly seen. Note distinct folding of the nuclear membrane and suggestion of nucleoli. Clumping of immature cells in cutaneous smears was frequently seen (Wright's stain; ×650). *c* (Case 3). Cutaneous smear, wet technic. Note large Sternberg-Reed cell on left and folded nuclear membranes in pleomorphic cells in upper right. *d* (Same case). Cutaneous smear, wet technic. Note large pleomorphic histiocyte; below it is an eosinophil (both hematoxylin and eosin; ×850).

nodes, a nodular infiltration of the skin appeared and became universally distributed over the body. Examination at the clinic disclosed considerable degrees of excoriation and lichenification of the skin. Generalized adenopathy was noted. The liver was slightly enlarged, and the spleen was moderately enlarged. Diligent search of blood smears revealed a single immature monocyte. Biopsy of skin over the right scapula resulted in the diagnosis of Hodgkin's sarcoma. The patient received nitrogen mustard and x-ray therapy with moderate improvement. After treatment, biopsy of a nodule was made and wet touch

smears were prepared by immediate immersion of the slide in equal parts of ether and alcohol after the smear was made.

Sections of the skin revealed infiltration of the dermis by dark-staining cells with lobed nuclei. There were occasional giant cells with multilobulated nuclei characteristic of Sternberg-Reed cells. Cutaneous smears stained with hematoxylin and eosin provided several examples of these giant connective-tissue cells, many in different stages of development (fig. 2*c* and *d*).

The patient died of bacteremia 3 years after the onset of symptoms. Necropsy revealed Hodgkin's disease chiefly in the skin and superficial lymph nodes. Verrucous endocarditis was present, with multiple emboli and infarctions in the principal organs of the body.

Case 4.—A 46-year-old man was first seen at the clinic in June, 1947. He had noted development of bilateral cervical adenopathy in 1941. In 1943, a diagnosis of "probable" Hodgkin's disease had been made by his home physician and the patient had received x-ray therapy without benefit. In 1946, he had noted erythema, which persisted on the scalp; at the same time, night sweats had appeared. Examination revealed moderately enlarged discrete hard cervical lymph nodes bilaterally. Both the liver and spleen were enlarged 2 cm. below the costal margins. Some redness of the scalp was present. Biopsy of a left cervical lymph node revealed lymphosarcoma. X-ray therapy was administered.

On his return in February, 1948, the patient said he had improved except for recent progression of the erythema of the scalp, which now was found to contain multiple firm subcutaneous nodules. A nodule was excised from the scalp and touch smears were made. Sections of the nodule showed diffuse infiltration of lymphocytes, together with somewhat larger and lighter-staining cells (fig. 3*a*). Few mitotic figures were noted. The infiltrating cell was immediately identified, however, on study of the cutaneous smear (fig. 3*b*). Various stages of cellular development were seen, ranging from cells in mitosis, through large cells with large nuclei containing fine pale-staining chromatin and numerous vesicular nucleoli, through more adult cells and finally to the small adult lymphocyte. A diagnosis was made of lymphosarcoma of the lymphoblastic type.

The patient again was treated with nitrogen mustard without much benefit and he received more x-ray therapy at home. The patient died in August, 1948. There was no information as to the cause of death.

Case 5.—A 65-year-old man first noted small reddish nodules appearing in the skin over the thorax in 1941. These nodules gradually increased in size during the next 6 years in spite of electric cautery and x-ray and radium therapy given by his home physicians. Examination at the clinic in December, 1947, disclosed 10 small purplish-red indurated tumors that formed a plaque measuring 3 by 5 cm. in diameter in the skin of the trunk on the left side posteriorly. Results of quantitative and morphologic studies of the blood were within normal limits.

Sections of skin revealed diffuse infiltration of cells extending from the epidermis to the subcutis. These cells were identified as lymphocytes and were intermingled with somewhat larger cells; no mitotic figures were apparent (fig. 4*a*). Cutaneous smears revealed that about half of the infiltrating cells were small and large lymphocytes; the balance of the cells were larger and exhibited immaturity extending back to the stem cell (fig. 4*b* and *c*). Since the predominant cells were lymphocytes of the mature or slightly immature type, a diagnosis was made of lymphosarcoma of the lymphocytic type.

In comparing these smears with those in case 4, a greater preponderance of immature cells is noted in case 4. This is to be expected in metastatic lesions, whereas the lesions in case 5 had spread only locally during a period of more than 6 years.

Case 6.—A 40-year-old man gave a history of vague discomfort in the left side of the thorax beginning 5 months previously and becoming progressively worse. Three months

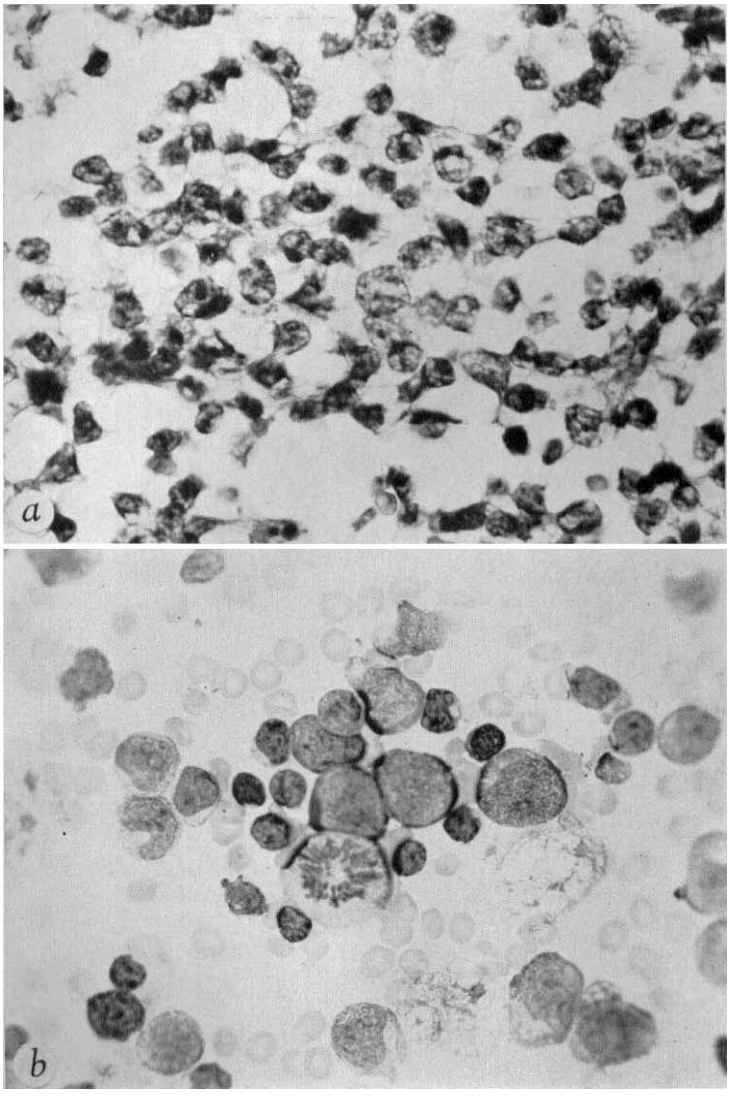

FIG. 3*a* (Case 4). Section of skin in lymphosarcoma. It is difficult to identify the infiltrating cells. Epithelioid cells predominate and the darker-staining pathologic cells are indistinctly seen (hematoxylin and eosin; ×600). *b* (Same case). Cutaneous smear. The infiltrating cells are undistorted. The predominating cell has a large nucleus with pale chromatin and vesicular nucleoli. Lymphocytes are seen in all phases of development from stem cells to small mature forms. Peripheral blood showed nothing abnormal. Compare *a* and *b* (Wright's stain; ×600).

before admission he had noted progressive dyspnea, and for 1 month he had suffered from fever. A diagnosis of viral pneumonia had been made a month before admission and he had received sulfadiazine and penicillin. The patient was hospitalized when he came to the clinic because he was extremely ill. Left pleural effusion was present. Repeated leukocyte counts disclosed values of less than 2,000 cells per cubic millimeter of blood; a shift to the

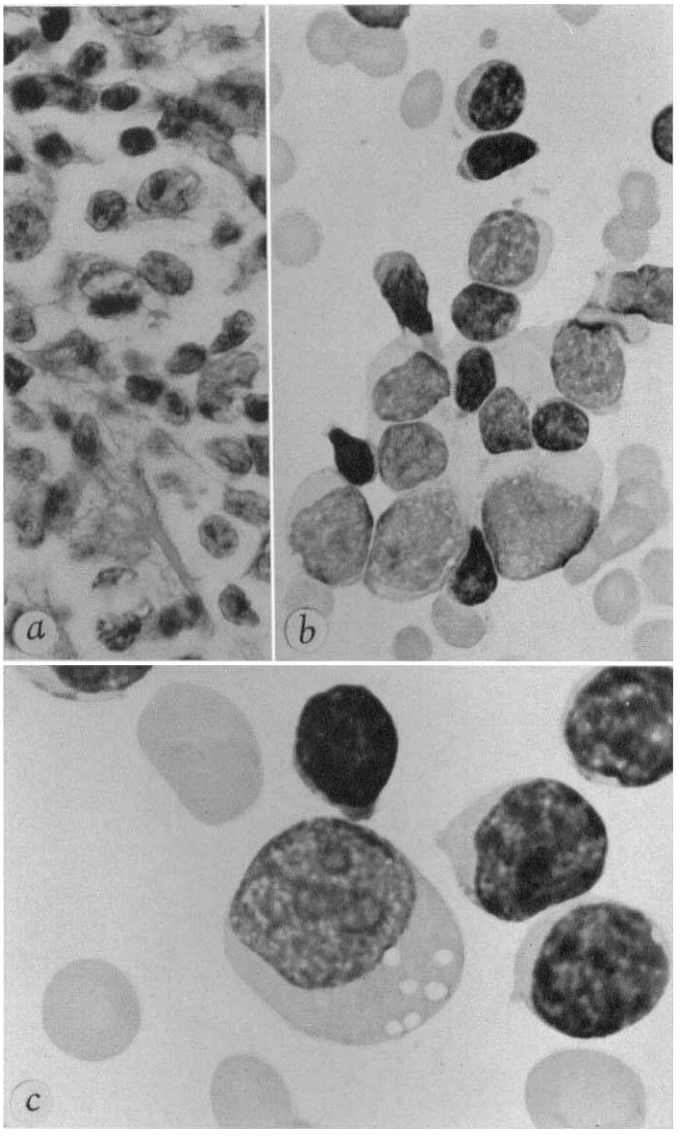

FIG. 4*a* (Case 5). Section of skin in lymphosarcoma. The infiltration extended from the epidermis to the subcutis; the infiltrating cells appear to be lymphocytes of different sizes (hematoxylin and eosin; ×920). *b* (Same case). Cutaneous smear at same magnification as *a* for comparison. Note high proportion of immature cells. All cells are of the lymphocytic series. Peripheral blood showed nothing abnormal (Wright's stain; ×920). *c* (Same case). Cutaneous smear; note beautiful example of a stem, or blast, cell showing three distinct nucleoli. The other cells are adult lymphocytes and erythrocytes (Wright's stain; ×1,800).

left was present in the granulocytes but no myeloid immaturity was evident. Results of examination of sternal marrow were interpreted as diagnostic of acute leukemia.

Shortly after admission purplish nodules from 0.5 to 1 cm. in diameter appeared on the skin of the thorax. Sections from 1 of these nodules revealed rather circumscribed infiltration of cells into the deep portion of the cutis; these cells appeared to be adult and immature leukocytes (fig. 5*a*). Cutaneous smears showed a great concentration of cells so immature that the type of differentiation could not be determined (fig. 5*b*). At this time immature cells were found with increasing frequency in smears of the peripheral blood. Study of the sections of skin suggested the diagnosis of leukemia or lymphosarcoma. The cutaneous smears showed acute leukemic infiltration. The course of the patient was slowly downward, with appearance in the peripheral blood of some stem cells, atypical young lymphocytes and occasional young monocytes. The leukemia could not be classified as to type. The patient died 4 months after admission.

Necropsy revealed a spleen that was four times the normal weight. The skin of the arms and left leg contained numerous small indurated elevated nodules, the largest measuring 1 cm. in diameter. The mediastinal lymph nodes were enlarged. The pathologist reported that these nodes disclosed focal lymphocytic accumulations; the same description was given to the spleen and to the specimens of infiltrated skin.

This case is an example of acute leukemia in which specific infiltration of leukemic cells into the skin occurred at a time when such cells were seen only rarely in the peripheral blood.

Case 7.—A 63-year-old woman first noted a small pigmented mass on the right ankle in August, 1947. The mass gradually grew until it was excised elsewhere in December, 1947; a pathologic diagnosis of malignant melanoma was made. In May, 1948, the patient noticed the appearance of another violaceous nodule on the right ankle. She came to the clinic in July, 1948, where the nodule was excised and touch smears were made.

Study of sections verified the diagnosis of malignant melanoma (fig. 5*c*). Cutaneous smears revealed a great concentration of large cells whose cytoplasm contained a multitude of small dark-staining granules. There was abundant evidence of amitotic division and many melanomatous cells with multiple large nuclei containing dark-staining chromatin and nucleoli (fig. 5*d* and *e*).

Case 8.—A 48-year-old man had noted bilateral swelling in the neck of 6 weeks' duration. Three weeks before admission, biopsy of a cervical lymph node done elsewhere resulted in the diagnosis of highly anaplastic metastatic carcinoma. On admission to the clinic, the patient exhibited bilateral supraclavicular and cervical adenopathy, with matted, firm and moderately enlarged lymph nodes. Review of the biopsy specimen taken previously resulted in the diagnosis of grade 4 squamous cell epithelioma. The patient was treated with x-rays in March and May, 1948.

In July, 1948, he returned because of edema and a pruritic papular eruption that first appeared on the right arm a month before and then extended to the skin over the sternum. Biopsy of a papule on the right arm gave a diagnosis of a grade 4 neoplasm, probably metastatic (fig. 6*a*). Cutaneous smears revealed clumps of large cells with extremely large hyperchromatic nuclei containing multiple nucleoli (fig. 6*b*).

Case 9.—A 62-year-old woman had a right mastectomy in January, 1946, followed by x-ray therapy. In June, 1946, a cyst had appeared in the left temporal region. This cyst ruptured and drained serosanguineous fluid; the sinus persisted. In January, 1948, small nodules had appeared in the skin about the scar on the thorax. X-ray therapy was given to this area and also to the temporal region. The patient was first seen at the clinic in March, 1948, at which time a specimen of skin was excised from the indurated region in the scalp above the left ear.

Sections of skin showed the presence of rather large dark-staining cells infiltrating the dermis in a linear fashion or arranged in groups. Cutaneous smears showed undifferentiated

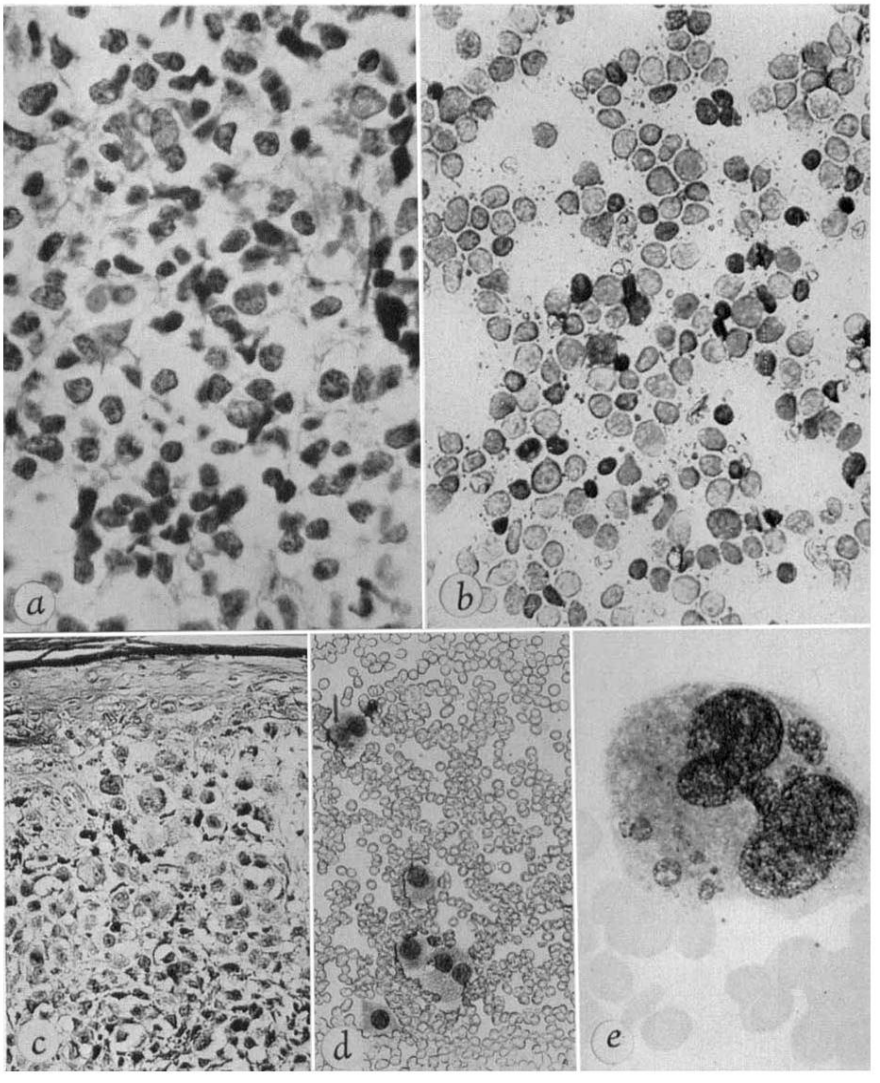

FIG. 5*a* (Case 6). Section of skin in acute leukemia. The infiltrating cells stain with different intensities but cannot be completely identified (hematoxylin and eosin; ×580). *b* (Same case). Cutaneous smear showing acute leukemic infiltration. Note the even distribution of undistorted cells; the predominating cells are so immature that the type of differentiation cannot be determined. Occasional immature cells were found in the peripheral blood (Wright's stain; ×250). *c* (Case 7). Section of skin in malignant melanoma. Note dense infiltration of large cells with large nuclei and granular cytoplasm (hematoxylin and eosin; ×125). *d* (Same case). Cutaneous smear. Multiple nuclei are visible in the melanotic cells as a result of imperfect division. Note nucleoli in cell (1) (Wright's stain; ×180). *e* (Same case). Cutaneous smear. Note melanomatous cell undergoing division and the granular nature of the cytoplasm (Wright's stain; ×900).

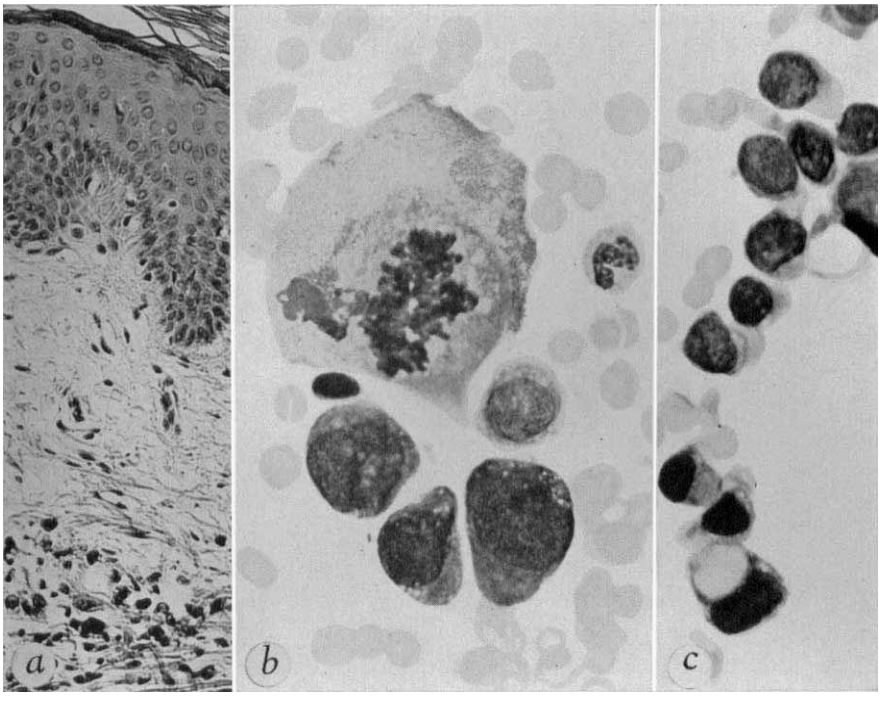

FIG. 6*a* (Case 8). Section of skin in metastatic grade 4 epithelioma. Large dark-staining cells are seen in the lymphatic and vascular spaces in the dermis (hematoxylin and eosin; ×200). *b* (Same case). Note mitotic figure; metastatic epithelial cells are large compared to the nonfilamented neutrophil at the right (Wright's stain; ×700). *c* (Case 9). Cutaneous smear. The infiltrating cells appear to have secretory globules in their cytoplasm (Wright's stain; ×625).

cells with what appeared to be vacuoles in the cytoplasm and large nuclei with nucleoli (fig. 6*c*). Staining with mucicarmine revealed that the vacuoles absorbed the carmine, thus identifying the cellular secretion as mucin. A diagnosis was made of metastatic adenocarcinoma.

COMMENT

This study indicates that cutaneous smears are a valuable adjunct in a study of the morphologic detail of cells infiltrating the dermis. Invading malignant cells can be distinguished easily from normal cells in the smear because they are not greatly distorted by the stroma of the dermis. The atypical features of neoplastic cells observed included large size, increased ratio of nuclear volume to cytoplasmic volume, presence of nucleoli and variations in density of chromatin, ranging from the fine, pale-staining chromatin of immature lymphoid and myeloid cells to the hyperchromatic chromatin of carcinomatous cells. Evidence of cellular activity, such as secretion in adenocarcinomatous cells, may be noted.

Smears of the skin were of no aid in the diagnosis of inflammatory dermatoses typified by infiltration of the skin with cells normally encountered there. In these

cases, which were in the majority, study of sections of skin provided the best method of arriving at a diagnosis.

The contribution of the cutaneous smear as a diagnostic aid was demonstrated in the study of conditions in which abnormal cells had infiltrated into the dermis. In smears in such cases, the infiltrating cells were clearly depicted, undistorted and free of the confusing cellular stroma of the dermis. Many features of these cells were noted in the smears which were not at once obvious on study of the sections, so that more exact cytologic diagnoses were possible in several cases.

The malignant cells found in cutaneous smears may appear as the result of (1) primary autochthonous origin from cells in the dermis itself, (2) extension of an underlying malignant process and (3) lymphatic or hematogenous seeding of malignant cells into the dermis from a remote primary malignant lesion.

The interpretation of cutaneous smears requires experience but once this is gained the test has great practical value. With increasing emphasis on cytologic diagnosis in modern pathology, this procedure is destined to come into greater use. It is possible that cutaneous smears will permit more knowledge to be gained concerning certain diseases. Thus, in 3 cases of mycosis fungoides, cells of the histiocytic system appeared to be primarily involved.

The value of cutaneous smears as an adjunct to the usual methods of cutaneous biopsy is illustrated by a comparison of equally enlarged photomicrographs of sections and smears (see figs. 3*a* and *b* and 4*a* and *b*).

The preparation of cutaneous smears is simple. Three to six slides can be smeared in a minute when the specimen of skin is excised; the entire staining process can be completed in 6½ minutes. Any stain used to demonstrate specific features in sections of skin may be applied to the smears. The use of cutaneous smears is indicated in all cases in which infiltration of the skin by abnormal cells is suspected.

The speed of this method compares favorably with that of fresh frozen sections and may give needed information long before those specimens prepared by routine methods are available for study.

The skin is the most accessible organ of the body. Infiltration into it is sometimes the first sign of hitherto unsuspected malignant disease. Early performance of biopsy with smears of such lesions may bring to light pathologic processes inaccessible to routine diagnostic means.

SUMMARY AND CONCLUSIONS

Sections of skin and cutaneous smears in a series of 176 cases were studied in an attempt to evaluate cutaneous smears as an aid in the diagnosis of certain lesions of the skin. These cases represented 52 distinct types of cutaneous disease. Results of cutaneous smears were normal or nonspecific in 135 instances, whereas the smears in 41 cases revealed the presence of neoplastic disease. The diagnosis in 15 of these cases was more specific than could be obtained by study of sections of skin. In 6 cases of mycosis fungoides and in 1 case of Hodgkin's disease, smears failed to reveal neoplastic cells.

The cutaneous smear appears to be a simple method of obtaining cells infil-

trating the dermis in an undistorted state for microscopic study. The technic employed was the impression of freshly cut pieces of skin on glass slides. The slides were dried in air and treated with Wright's stain for 1½ minutes. A buffer solution then was added and allowed to act for 5 minutes. The slides were washed and dried.

Smears of skin in diseases not characterized by the infiltration of abnormal cells revealed erythrocytes, lymphocytes, blood and tissue leukocytes and fibers of collagen and elastin. Malignant cells could be distinguished from normal cells in cutaneous smears by numerous characteristics according to the type of abnormal cell present. Immaturity of cells of the lymphoid, myeloid and histiocytic series was evidenced by large cells having a large ratio of nucleus to cytoplasm, by variations in arrangement of chromatin according to the cellular type and by the presence of nucleoli. Some cells showed secretory activity.

Cutaneous smears showed the distribution of abnormal cells and often permitted a definite diagnosis when study of sections of skin resulted in a less specific diagnosis.

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